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Segregation Analysis of Alcoholism in High Density Families: A Replication

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We have previously reported segregation analysis of alcoholism in 35 multigenerational families, each ascertained through a pair of male alcoholics by using the mixed model implemented by POINTER. This analysis suggested that liability to alcoholism was, in part, controlled by a major effect with or without additional multifactorial effects. The hypothesis that the major effect was explained by a single genetic locus with strictly mendelian transmission was rejected. The purpose of the present analysis was to use the regressive model implemented by the REGD program from the Statistical Analysis for Genetic Epidemiology computer package (S.A.G.E.) to confirm by replication that a major effect was present in these 35 families. Evidence for the major effect found in Pointer was replicated in the present analysis by using S.A.G.E. Also, we found strong evidence for parental effects that were independent of the major locus transmission from ancestral relatives to children. Mendelian transmission of this major effect was rejected when models incorporated parental effects. When the major effect was calculated adjusting for parental phenotypes, the relative risk of affection for children was about twice as high with affected parents vs. unaffected parents.

KEY WORDS: alcoholism, regressive models, segregation analysis

INTRODUCTION

Familial transmission of alcoholism has clearly been established [Hill et al., 1977; Cloninger et al., 1978; Cotton, 1979]. The morbid risk to relatives of alcoholics appears to be three to five times higher than the risk to individuals in the general population when all of the studies are combined [Cotton, 1979]. The high rates of transmission seen in alcoholic families are probably not due entirely to genetic factors [Lester, 1988; Peele, 1986; Hill et al., 1986]. Recognizing the complex interplay between genetic factors on the one hand and environmental triggers on the other [Hill et al., 1986], we began collecting high-risk pedigrees as part of a large scale family study (Cognitive and Personality Factors Family Study [CPFFS]). Pedigree studies of this type afford the opportunity to study both affected and unaffected high-risk relatives in the absence of other major comorbidity given careful selection. In this way, the proportion of the variance in the underlying liability to alcoholism determined by genetic factors can be investigated even when phenotypic variation varies by gender and developmentally.

Previously, we performed a mixed model segregation analysis on 35 multigenerational families each ascertained through a pair of male alcoholics with no other comorbidity [Aston and Hill, 1990]. The results of that analysis suggested that the liability to alcoholism is, in part, controlled by a major effect with or without additional multifactorial effects. This major effect was not due to a single major locus, inasmuch as Mendelian transmission of the major effect was rejected. While a Mendelian major effect was not found, nevertheless, one interpretation of the findings might be that the underlying liability to alcoholism is oligogenic, i.e., two or more Mendelian loci may be responsible for the major effect being manifest. Clearly, other explanations are possible, such as the presence of phenocopies, or sex-dependent differences in the underlying liability model, or perhaps heterogeneity within the alcoholism phenotypes observed in this family study. Nevertheless, the importance of this finding warranted repeating the analysis, utilizing the regressive models implemented in the Statistical Analysis for Genetic Epidemiology (S.A.G.E.) computer package [Sorant et al., 1991] to analyze these same 35 families.

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DATA

Family Data

Although a larger data set is currently available, the same 35 families used for the previous publication [Aston and Hill, 1990] were analyzed. These 35 families were recruited as part of the Cognitive and Personality Factors Family Study of alcoholism initiated in 1984. Families were ascertained through a proband set consisting of both a male Caucasian index case who was currently attending a treatment center for alcoholism and a brother who met criteria for a lifetime diagnosis of alcoholism. Only those families with minimal psychiatric comorbidity (families were excluded where the proband had a first-degree relative with schizophrenia or recurrent depression) were included. Families were extended to include all first-, second-, and third-degree relatives. Consequently, the 35 families included 217 first-degree relatives (excluding the proband set), 407 second-degree relatives (379 with a diagnosis), and 422 third-degree relatives (295 with a family history diagnosis). Each of the 35 pedigrees included 32 individuals on average.

In order to replicate the conditions under which our previous findings were obtained using Pointer, we included only male sibs in the present analysis. Family members were acquired as a 2-stage process in the CPFFS study emphasizing males first and only later including females. Therefore, at the time the previous analysis was completed a disproportionate number of sibs were males. Future plans include extending the segregation analysis to utilize all female sibs as well to test for sex effects.

Clinical Data

Direct clinical interviews were conducted with the index case, with the obligate affected (alcoholic) brother, and, where possible, with a third brother (affected or unaffected) and both parents. First, a structured psychiatric interview was administered by a trained clinician. This interview included the Diagnostic Interview Schedule [Robins et al., 1981], enabling determination of whether or not the subject met a lifetime diagnosis for definite alcoholism on the basis of DSM-III and Feighner et al. [1972] criteria (note that the DSM-III was the current nomenclature in use when the study began and was retained for uniformity of diagnostic procedure). In addition, each symptom was dated for the earliest point in time at which it occurred. Thus, the age of onset for definite alcoholism could be estimated. An unstructured follow-up interview administered by a second clinician allowed for the determination of the "best estimate" diagnosis of the presence or absence of specific psychiatric disorders including alcoholism.

Family history information was systematically obtained for all second-degree relatives of the proband set and for those first-degree relatives who were deceased or did not participate in the direct clinical interviews. The family history information was derived from administration of the Family History of Physical and Mental Health Problems (FHPMHP) developed by one of the authors (Hill, unpublished).

The FHPMHP is a brief screening instrument that asks the respondent to describe his or her family structure for all first and second-degree family members. Once it has been determined that the respondent has knowledge of a particular family member's status, he/she is asked if that individual has had psychological, alcohol, or medical problems. Follow-up questions have been formulated to determine the accuracy of the respondents' labeling of relatives. When used in the context of a pedigree study and administered to all living members of the pedigree, multiple informants are available. The instrument has been validated utilizing direct diagnostic assessments of persons for whom family history data have been obtained and sensitivity and specificity determined [Smith, unpublished Ph.D. dissertation]. Specificity for the instrument is 94% with a sensitivity of 68%. This compares favorably with family history methods which yield sensitivity in the range of 54–60% [Orvaschel et al., 1982; Andreasen et al., 1977].

In general, presence of alcoholism diagnosed by family history alone was based on reports of at least 2 of the interviewed family members reporting objective problems associated with drinking (e.g., arrests, loss of job, or objections from family). The exception was for third-degree relatives where only one report was available. Family history information was also available for individuals who participated in the direct, face-to-face, clinical interviews. This provided a measure of the validity of the family history information for those individuals not interviewed. This also provided an assurance that those individuals interviewed were not underreporting symptoms of alcoholism. In a few cases, family history information was used together with Feighner et al. [1972] criteria of self-reported symptoms to make the final consensus diagnosis. Validity data have been calculated and sensitivity found to be over 90% [Smith, unpublished Ph.D. dissertation]. However, the phenotype was determined for first-degree relatives by direct, in-person, clinical interviews in most cases.

METHODS

Segregation analysis utilizing the regressive models [Bonney, 1986] was applied to analyze 35 multigenerational families each ascertained through a pair of male alcoholics. The regressive models represent an extension of the conventional logistic regression model for family data [Demenais, 1991]. These models allow genetic components to be incorporated under a simple Markovian dependence structure where the risk to an individual is written as a function of his/her own observed covariates and the phenotypes of his/her relatives [Bonney, 1984, 1986].

The regressive models are implemented in the REGD program of the S.A.G.E. computer package [Sorant et al., 1991]. Under the regressive models, 3 qualitative "types," g_i = AA, Aa, aa [Go et al., 1978; termed "ousiotype" by Cannings et al., 1978], were employed as the underlying factors for the phenotype (outcome); these ousiotypes are considered to be transmissible between generations. Thus, the ousiotype can allow both Mendelian and non-Mendelian transmission; genotypes are the special case of ousiotypes in which the transmission occurs in a Mendelian fashion. If one as-

sumes A and a to be the affected allele and the unaffected allele (at a major locus), respectively, there are several parameters which can be estimated, including q, the frequency of autosomal disease gene A; β_{gi}, baseline risks (at birth) of being affected for the 3 underlying ousiotypes, AA, Aa, and aa; δ_{p1}, the risk of the disease if the person's parent is affected; and δ_{p2}, the risk of disease if the person's parent is unaffected. δ_{p1} and δ_{p2} are additional parental effects, independent of the major locus transmission from parent to child. If the person's parent is affected, the risk of the disease is modified by δ_{p1}; if the parent is unaffected, it is modified by δ_{p2}; and if the parent is missing, the risk remains unchanged. Therefore, y_i, the logarithm of the odds of being affected (qualitative trait) for individual i with ousiotype g_i will be

$$y_i = \beta_{gi} + \delta_{p1}Z_{p1} + \delta_{p2}Z_{p2}$$

where an unsymmetric coding scheme, i.e., affected, unaffected, or missing is used in contrast to Bonney's [1986] symmetry on the logit scales where the risk for the disease with a given ousiotype is increased and decreased by the same quality (δ). Two dummy variables Z_{p1} and Z_{p2} are utilized to code the parent's phenotypes. These variables, Z_{p1} and Z_{p2}, are elements of a column vector Z_p, so that when primes are used to denote transposes,

$Z_p = (1,0)'$ if the parent is affected
$Z_p = (0,1)'$ if the parent is unaffected
$Z_p = (0,0)'$ if the parent is missing.

Since we have introduced 2 dummy variables instead of one in the parental adjustment method for each child's affection status, the increased risk (for the disease) among children of affected parents or the decrease among children of unaffected parents could be different in equality, i.e., different regression coefficients can be estimated for these 2 dummy variables (Z_{p1}, Z_{p2}).

Population birth prevalence cannot be automatically incorporated into the current version of REGD. This limitation may lead to inaccurate parameter estimation, especially in small sample sizes. Lustbader et al. [1992] have proposed a formulation to modify the regressive models to incorporate population prevalences as a covariate in the analysis, by setting:

$$y_i = \beta_{gi} + \log\left(\frac{r_k}{1 - r_k}\right) + \delta_{p1}Z_{p1} + \delta_{p2}Z_{p2}$$

Morbid risks (r_k) were determined based on the individual's age and sex and computed using the life-table method of Culter and Ederer [1958] and incorporating incidence data reported by Eaton et al. [1989]. These were the same risks as previously reported [Aston and Hill, 1990]. Individuals are partitioned into one of 8 classes called liability classes. Each class is assigned a unique risk. Table I displays the assigned risks for each liability class (k, from 1 to 8).

TABLE I. Classes of Morbid Risk for Alcoholism

Class(k)	Age (years)	Sex	Morbid risk (r_k)
1	0–29	Males	0.0517
2	30–44	Males	0.0933
3	45–64	Males	0.1091
4	65+	Males	0.1191
5	0–29	Females	0.0101
6	30–44	Females	0.0160
7	45–64	Females	0.0190
8	65+	Females	0.0217

For each restricted model tested, the most likely values of parameters are computed and corresponding maximum likelihoods are compared (standard likelihood ratio test) with that of the more general model (with more parameters being estimated). Akaike's [1974] Information Criterion (AIC) was used to select the most parsimonious model among equally likely models.

RESULTS

Testing of Genetic Models

The results of the present analysis were based on the regressive model and were obtained through the computer program REGD in the S.A.G.E. package [Sorant et al., 1991]. In all analysis presented here, the log likelihood of the model was conditioned on the pair of probands assuming a single multiplex ascertainment correction. The transformed morbid risk [$\log(r_k/(r_k - 1))$] was modeled as a covariate with a fixed coefficient of 1.

Table II shows the results of segregation analysis of the 35 multigenerational pedigrees without considering parental adjustment. Under the regressive logistic model with only a major effect, the "most general" model (model 7, Table II) allows 7 parameters to vary and be estimated. This yields values close to a Mendelian transmission ratio: $\tau_{AA} = 1.00$, $\tau_{Aa} = 0.610$, and $\tau_{aa} = 0.066$. When compared with model 7 of Table II, the "no major effect" model (model 1, Table II) was rejected ($\chi^2 = 91.61$, df = 6, $P < 0.001$). The "non-Mendelian" model (model 6, Table II) is one in which the non-Mendelian transmission ratios were assumed, i.e., $\tau_{AA} \neq 1.0$, $\tau_{Aa} = 0.5$, and $\tau_{aa} = 0.0$, and the 3 baseline risk parameters for accommodating the mode of inheritance were estimated. The "non-Mendelian" model fits the data well ($\chi^2 = 1.42$, df = 2, $P > 0.5$). Furthermore, the "general Mendelian" model (model 5, Table II) was also found to be consistent with the data when compared with model 6 of Table II, which assumes non-Mendelian transmission $\tau_{AA} \neq 1.0$, $\tau_{aA} = 0.5$, and $\tau_{aa} = 0$ ($\chi^2 = 0.66$, df = 1, $P > 0.1$). All 3 specific Mendelian models—dominant (model 2, Table II), additive (model 3, Table II), and recessive (model 4, Table II)—were found to fit the data equally well when compared with the "general Mendelian" model ($\chi^2 = 2.47$, df = 1, $P > 0.1$; $\chi^2 = 2.33$, df = 1, $P > 0.1$; and $\chi^2 = 0.02$, df = 1, $P > 0.75$, respectively); thus, each of these 3 models could not be rejected. As can be seen, several models with either Mendelian or non-Mendelian transmission provided equally likely descriptions. A recessive Mendelian model offers the lowest AIC value when compared with other models in Table II only.

TABLE II. Results From Regressive Logistic Models Using 35 Multigenerational Families Ascertained Through a Pair of Male Alcoholics Without Considering Parental Adjustment*

Model	Baseline risk for τ_{AA}	τ_{Aa}	τ_{aa}	q_A	AA	Aa	aa	P[a]	−21nL	AIC
1. No major effect	—	—	—	[1.00]	−1.450	$=\beta_{AA}$	$=\beta_{AA}$	1	737.056	739.056
2. A dominant Mendelian	[1.0]	[0.5]	[0.0]	0.054	2.997	$=\beta_{AA}$	0.237	3	650.005	656.005
3. A additive Mendelian	[1.0]	[0.5]	[0.0]	0.059	5.347	2.770	0.192	3	649.862	655.862
4. A recessive Mendelian	[1.0]	[0.5]	[0.0]	0.441	2.789	$=\beta_{aa}$	−0.625	3	647.554	653.554
5. General Mendelian	[1.0]	[0.5]	[0.0]	0.474	2.710	−1.726	−0.182	4	647.535	655.535
6. $\tau_{Aa} = 0.5$, $\tau_{aa} = 0$ Non-Mendelian major effect	0.856	[0.5]	[0.0]	0.293	3.724	1.059	−2.025	5	646.873	656.873
7. Most general	(1.0)	0.610	0.066	0.477	−0.693	−1.404	2.876	7	645.449	659.449

*Brackets denote parameter values fixed by a given model. Parentheses denote parameter values which converged to a boundary value fixed by a given model.
[a]Number of parameters estimated.

Testing of Residual Parental Effects Alone

We next examined whether a residual parental effect alone can explain the transmission pattern of alcoholism in these pedigrees. Table III lists the results for testing parental effects (δ_p). Model 1 of Table III includes a random environmental effect and the residual effects from parents. When comparing model 1 of Table III vs. model 1 of Table II, which includes only a random environmental effect, we found that the introduction of parental adjustment (δ_{p1}, δ_{p2}) significantly improved the fit of the models to the data ($\chi^2 = 191.57$, df $= 2$, $P < 0.001$). The considerably improved fit of model 1 of Table III over model 1 of Table II indicates a significant parents-to-offspring transmission (genetic or nongenetic). The further inclusion of an arbitrary major gene effect (model 5, Table III) yielded a still much better fit with the data when compared to model 1 of Table III with random environmental and parental effects ($\chi^2 = 24.91$, df $= 6$, $P < 0.001$). The significantly improved fit of model 5 of Table III indicates that parental effects alone were not adequate to explain the familial aggregation of alcoholism in these families. In other words, this suggests that the major effect is a necessary part of the model.

Testing of Genetic Models Plus Parental Effects

We then tested the significance of the residual parental effect under the hypothesis of a major effect for the recessive Mendelian model, the "general Mendelian" model, the "non-Mendelian" model, and the "most general" model, i.e., those which were consistent with the data in our first analysis (Table II). The introduction of 2 additional parameters (δ_{p1}: effect of affected parent and δ_{p2}: effect of unaffected parent) significantly improved the maximum likelihoods (models 2, 3, 4, and 5, Table III) in comparison to each of the simpler models (models 4, 5, 6, and 7, Table II). Thus, for the recessive Mendelian model, the "general Mendelian" model, the "non-Mendelian" model, and the "most general" model, when we added the 2 covariates representing parental phenotypes, the maximum log likelihoods were significantly improved by $\chi^2 = 111.03$, df $= 2$, $P < 0.001$; $\chi^2 = 111.32$, df $= 2$, $P < 0.001$; $\chi^2 = 112.16$, df $= 2$, $P < 0.001$; and $\chi^2 = 124.87$, df $= 2$, $P < 0.001$. For these 4 models (2, 3, 4, and 5, Table III), the estimates of the parental adjustment (δ_{p1}, δ_{p2}) are both positive and significantly greater than zero ($P < 0.001$). In addition, all of the 4 models with additional parameters for parental adjustment have lower

TABLE III. Results From Regressive Logistic Models Using 35 Multigenerational Families Ascertained Through a Pair of Male Alcoholics With Adding Parental Adjustment*

Model	Baseline risk for τ_{AA}	τ_{Aa}	τ_{aa}	q_A	AA	Aa	Parental adjustment aa	δ(unaff)	δ(aff)	P[a]	−21nL	AIC
1. No major effect plus δ_p	—	—	—	[1.00]	−0.511	$=\beta_{AA}$	$=\beta_{AA}$	1.166	1.896	3	545.491	551.491
2. A recessive with δ_p	[1.0]	[0.5]	[0.0]	0.027	4.524	$=\beta_{aa}$	−1.215	1.506	2.254	5	536.527	546.527
3. General Mendelian with δ_p	[1.0]	[0.5]	[0.0]	0.001	2.919	2.205	−1.263	1.518	2.191	6	536.220	548.220
4. $\tau_{Aa} = 0.5$, $\tau_{aa} = 0$ Non-Mendelian major effect with δ_p	0.462	[0.5]	[0.0]	0.021	5.230	−0.013	−1.399	1.549	2.179	7	534.718	548.718
5. Most general with δ_p	0.007	0.438	(0.0)	0.359	3.329	−0.217	−0.488	1.072	1.790	9	520.584	538.584

*Brackets denote parameter values fixed by a given model. Parentheses denote parameter values which converged to a boundary value fixed by a given model.
[a]Number of parameters estimated.

TABLE IV. Expected Predicted Risks for Alcoholism

Age (years)	Sex	Predicted risk: Unaffected parents (%)	Affected parents (%)	Missing parents (%)
0–29	Males	25.2	59.2	3.2
30–44	Males	38.9	73.2	5.8
45–64	Males	43.1	76.5	6.8
65+	Males	45.5	78.2	7.5
0–29	Females	5.9	21.3	0.6
30–44	Females	9.1	30.2	1.0
45–64	Females	10.7	34.0	1.1
65+	Females	12.1	37.1	1.3

AIC values. The difference in likelihood of non-Mendelian transmission $\tau_{AA} \neq 1.0$, $\tau_{aA} = 0.5$, and $\tau_{aa} = 0$ with parental adjustment (model 4, Table III) when compared with the "most general" model with parental adjustment (model 5, Table III) was significant ($\chi^2 = 14.13$, df = 2, $P < 0.005$); thus this model could be rejected. Similarly, models 2 and 3 of Table III, which are the recessive model with parental effects and general Mendelian model with parental effects, respectively, were also rejected when compared with model 5 ($\chi^2 = 15.94$, df = 4, $P < 0.005$ and $X^2 = 15.64$, df = 3, $P < 0.005$, respectively). As can be seen, the "most general" model with parental adjustment (model 5, Table III) offers the lowest AIC value, and therefore, would be considered the most parsimonious by that criterion.

Calculating the Expected Predicated Risks

Models with residual parental effects gave a statistically significant improvement in the fit in comparison with the corresponding ones without residual parental effects. The positive estimated coefficients (δ_{p1}, δ_{p2}) for parental adjustment indicate that the offspring have the increased risk as a result of either having affected parents or unaffected parents, though higher for the case of affected parents. Under the no major effect plus parental adjustment model (1, Table III), predicted risks are given in Table IV with either of 3 parental affection statuses (unaffected, affected, and missing) and 8 different combinations of age and sex. "Missing" parent refers to cases where there was no information being available for a parent, grandparent, or great grandparent to assign a diagnosis. In our pedigrees information was always available for the proband's parents (direct diagnostic interview). However, the probands' grandparents infrequently had missing information (less than 15% of cases). The higher risk for the children of unaffected parents as compared to the risk for the children whose parents are unknown is probably due to a fall off in sensitivity of the diagnostic methodology. The parents of the probands were interviewed in person while only one informant provided family history data for the grandparents and great grandparents of the probands. Obviously, the single informant family history produces reduced sensitivity for the grandparents in comparison to the information for the proband's parents.

DISCUSSION

Results of the complex segregation analysis using the regressive models implemented by the S.A.G.E. package suggests that the underlying liability to develop alcoholism is, in part, controlled by a major effect though not a single major Mendelian locus. Utilizing the AIC the most parsimonious models were selected. The model which assumes the most general non-Mendelian transmission was found to be consistent with the pedigree data when compared with the rest of Mendelian and non-Mendelian models. An important aspect of familial transmission of alcoholism might be the effect of the parental phenotype on the offsprings' likelihood of developing alcoholism due to possible modeling effects. Children living in homes where alcoholism is present might be more likely to become alcoholic simply due to the effect of mimicking the behavior of the parent. The impact of parental behavior has been demonstrated by Wolin et al. [1980]. They found that families could be characterized by the degree to which the alcoholic parent's behavior was disruptive of family "rituals." These families they termed "subsumptive" ones. This subsumptive type tended to transmit alcoholism to the next generation much more readily than "distinctive" ones, or those in which the parent's behavior was not disruptive of family holidays and rituals. More recent work by Stacy et al. [1991] on expectancy-behavior relations is also relevant in this context. Expectancy motivations have clear influence on the use of alcohol and drugs and can be transmitted within the family. Of course, indirect effects due to moderating variables associated with parental status (e.g., child's health care, diet) are potentially important as well. Therefore, we tested the significance of the residual parental effect under the hypothesis of either a major effect or no major effect. We found that the residual parental effect, though significantly improving the maximum likelihood estimation, was not sufficient by itself to explain the data obtained. Rather, the major effect was a necessary part of our explanation. This suggests that the phenotype of the offspring depends on both parents' ousiotypes (AA, Aa, or aa) as well as the parental affection status.

The major effect found may be due to a few major "loci" contributing to the liability for developing alcoholism resulting in non-Mendelian transmission. Our previous analysis using Pointer [Aston and Hill, 1990] also indicated evidence for a major effect that was non-Mendelian. In our previous report we suggested that a single Mendelian locus confounded by phenocopies might be a plausible explanation for the departure of the τ parameters from the expected values of 1.00. In the present analysis the τ parameter was 1.00 indicating that the presence of phenocopies is an unlikely explanation. However, the non-Mendelian major effect in the present analysis appears to be consistent with an oligogenic effect.

These results are interesting in view of previous reports suggesting that some families ascertained through male alcoholics show evidence for a major locus. Gilligan et al. [1987] found evidence for a major locus with a dominant mode of inheritance though they

did not report any departures from Mendelian transmission parameters for the major locus. In our previous report we noted that if a Mendelian major locus were to be fitted to the present data, the maximum likelihood estimates would suggest a nearly dominant mode of inheritance. However, in the present analysis we were not able to distinguish between modes of inheritance (dominant, additive/codominant, or recessive) inasmuch as the differences in fit of these models were not significant at the 0.05 level.

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